REMARKS

Request for Continued Examination

The present submission is a Request for Continued Examination (RCE) under 37 CFR §1.114(b), of U.S. Patent Application Serial No. 10/787,442. The Notice of Appeal for the above-named application was filed on March 13, 2008.

Claims 1, 2 and 10-12 are pending. Claim 1 has been amended. Claims 3-9 are canceled pursuant to a restriction requirement. Applicants expressly reserve the right to prosecute any withdrawn, canceled or deleted subject matter in other related patent applications. No new matter has been added.

Rejections from Office Action dated September 17, 2007

Rejections Under 35 U.S.C. §112

Enablement

The Examiner maintains the rejection of claims 1, 2 and 10-12 under 35 U.S.C. §112, first paragraph, because the specification while enabling for a fusion protein comprising polypeptide of SEQ ID NO: 2, does not reasonably provide enablement for all possible fusion proteins comprising variants and fragments including those that are at least 90% or 95% identical to SEQ ID NO: 2.

Applicants have amended claim 1 to recite "a fusion protein comprising a first polypeptide comprising a sequence of amino acid residues that is at least 90% identical to residues 41 to 148 of SEQ ID NO:2...". The amendment makes clear that the first polypeptide must comprise an amino acid sequence that is at least 90% identical to the sequence from amino acid 41 to amino acid 148 of SEQ ID NO: 2. Any variation within the polypeptide must be limited to modifications that retain at least 90% identity to a defined region, i.e., from amino acid residues 41 to 148 of SEQ ID NO: 2. This language clearly and plainly does not permit six amino acid fragments, or unlimited variations.

The rejection essentially focuses two issues; the phrase "a polypeptide" and the presence of enabling disclosure for claims to a polypeptide comprising a sequence at least 90% identical specific amino acid residues. Claim 1 (and claims 2 and 10-12 by virtue of their dependency) are amended and clearly the phrase "a polypeptide"

in the context used in these claims is such that only a specified amount of variation is permitted, not the unlimited variation previously asserted by the Office. For example, in amended claim 1, the polypeptide must comprise an amino acid sequence that is at least 90% identical to the sequence from amino acid 41 to amino acid 148 of SEQ ID NO: 2. Any variation within the polypeptide must be limited to modifications that retain at least 90% identity to a defined region, i.e., from amino acid residues 41 to 148 of SEQ ID NO: 2. This language clearly and plainly does not permit six amino acid fragments, or unlimited variations. Likewise, claim 9 is further limited to modifications that are at least 95% identical to the sequence from amino acid 41 to amino acid 148 of SEQ ID NO: 2, and claims 11 and 12 cannot have any modifications. When "a polypeptide" is construed in the proper context, it is defined as a sequence of amino acid residues (e.g. 41-148 or 32-162) with limitations on the percent of modification clearly identified in the claim, and the claims do not read on any and all (i) protein variants with any number of deletions, substitutions, or additions and (ii) fragments of SEQ ID NO:2, including sequences only six amino acids in length. Thus, claims reasonably correlate to the scope of the enablement provided.

Second, the Examiner also maintained that while the specification discloses the biological function of the zalpha11 ligand (aka IL-21), applicants have not provided a correlation between the variants and the biological functions disclosed. It is the Examiner's belief that in the absence of such correlation, further guidance is required or undue experimentation would be required by one skilled in the art. Applicants maintain the claimed polypeptides are enabled and the Office is incorrect because (1) the interpretation is broader than is reasonable and (2) guidance for those skilled in art is provided in the specification for the claimed polypeptides.

The first aspect of applicants' argument is discussed in detail above, but applicants would point out that support for such a broad interpretation as the Office is using is not found in the application, for the simple reason that applicants never intended to make such a claim and therefore never described or enabled DNA encoding any and all amino acid sequences that were six amino acid residues long.

With regard to the second aspect, applicants assert the specification does provide the guidance necessary for one skilled in the art to do any routine

experimentation necessary to identify which polypeptides fall within the scope of the claims. Through the use of alignments of the previously-known cytokines related to zalpha11 ligand (Table 1) and the newly discovered human and mouse species of zalpha11 provided (SEQ ID NOS: 2 and 56, respectively), the specification describes structural and functional relationships within the cytokine family, and the present inventors establish the requisite guidance necessary for one skilled in the art to make and use claimed variants. As was previously stated in the Response to the Office Action dated January 12, 2007, applicants describe the protein family in detail; defining helices A-D and loop structures. For example, on pages 10-11 the specification discloses:

> In general, cytokines are predicted to have a four-alpha helix structure, with helices A, C and D being most important in ligand-receptor interactions, and are more highly conserved among members of the family. Referring to the human zalpha11 Ligand amino acid sequence shown in SEQ ID NO:2, alignment of human zalpha11 Ligand, human IL-15, human IL-4, and human GM-CSF amino acid sequences it is predicted that zalpha11 Ligand helix A is defined by amino acid residues 41-56; helix B by amino acid residues 69-84; helix C by amino acid residues 92-105; and helix D by amino acid residues 135-148; as shown in SEQ ID NO: 2. Structural analysis suggests that the A/B loop is long, the B/C loop is short and the C/D loop is parallel long. This loop structure results in an up-up-down-down helical organization. The cysteine residues are absolutely conserved between zalpha11 Ligand and IL-15, as shown in Figure 1. The cysteine residues that are conserved between IL-15 and zalpha11 Ligand correspond to amino acid residues 71, 78, 122 and 125 of SEQ ID NO: 2. Conservation of some of the cysteine residues is also found in IL-2, IL-4, GM-CSF and zalpha11 Ligand corresponding to amino acid residues 78 and 125 of SEQ ID NO: 2, as shown in Figure 1. Consistent cysteine placement is further confirmation of the four-helical-bundle structure. Also highly conserved in the family comprising IL-15, IL-2, IL-4, GM-CSF and zalpha11 Ligand is the Glu-Phe-Leu sequence as shown in SEQ ID NO: 2 at residues 136-138, as in Figure 1.

Not only does the specification describe and enable genera of variants, but species are described and enabled as well. The specification teaches which amino acids can vary from SEQ ID NO: 2 as much as 10%, and still result in a protein that is biologically functional, e.g. binds the zalpha11 receptor of SEQ ID NO:115.

As previously explained, the specification discloses at page 11:

> While helix A is relatively well-conserved between human and murine zalpha11 Ligand, helix C is more divergent. While both species have predominant acidic amino acids in this region, the differences may account for species specificity in interaction between zalpha11 Ligand and its "beta" type receptor, zalpha11. Loop A/B and helix B of zalpha11 Ligand are well-conserved between species; although no receptor subunit corresponding to IL-2Rα has yet been identified, conservation through this region suggests that it is functionally significant. The D helices of human and murine zalpha11 Ligand are also highly conserved. Zalpha11 receptor antagonists may be designed through mutations within zalpha11 Ligand helix D. These may include truncation of the protein from residue Gln_{145} (SEQ ID NO: 2), or mutations of Gln_{145} or Ile_{148} (of SEQ ID NO: 2; corresponding to Tyr_{124} in human IL-4) to residues such as Ala or Asp. Any mutation which disrupts the zalpha11 Ligand helical structure may abolish binding with its receptor and thus inhibit signaling.

Thus, the specification provides the skilled artisian with all the tools needed to make routine any experimentation necessary to demonstrate that a claimed polypeptide falls within the scope of the instant claims.

Moreover, it is not surprising that others using the disclosures and teachings in the instant specification have identified polypeptides comprising amino acid residues at least 90% identical to residues 41 (Gln) to 148 (Ile) as shown in SEQ ID NO:2 and that these polypeptides have the same activities as the presently claimed inventions, i.e. bind the cognate receptor and cause proliferation in an NK cell assay. It is well accepted that an applicant can use post-filing publications as evidence of the level of skill in the art at the time the application was filed (MPEP 2164.05), and that enablement is supported.

Applicants teachings combined with that which was known and available to those skilled in the art has resulted in publication of variants polypeptides that not only fall within the scope of the claimed invention but could be predicted using the guidance provided by the specification. For example, in December 2004, Cunningham et al., (PCT/US2004/018903 (published as WO 2004/112703)) describes several variant IL-21

polypeptides with 11 to 14 amino acid residue changes in the sequence between residues 32 and 162 of SEQ ID NO:2. Cunningham et al. used the polynucleotide and polypeptide sequences discovered and provided by present the inventors as the bases for their studies. Over a range of 131 amino acids, the percent identity between the variant and reference SEQ ID NO:2 is between ~89-92%. By comparing Figure 2 of Cunningham et al. to, for example, page 34 of the instant specification, one can see the changes made are either conservative or avoid the regions applicants' teach are important for activity. Analyses were performed using programs and assays described or similar to those described in the instant specification; many of which have been known to those in the art for years using commercially available reagents. Cunningham et al. provides evidence that applicants' specification provided an enabling disclosure for claims to polypeptides comprising a sequence of amino acid residues that are at least 90% identical to residues 41 (Gln) to 148 (Ile) as shown in SEQ ID NO:2 and polypeptides comprising a sequence of amino acid residues that are at least 90% identical to residues 32 (Gln) to 148 (Ile) as shown in SEQ ID NO:2.

The distinctive use of "a fusion protein comprising a first polypeptide comprising a sequence of amino acid residues that is at least 90% identical to residues 41 to 148 of SEQ ID NO:2" limits the modifications and variations that can be to any polypeptide that would fall within the scope of the claims, and these polypeptides are enabled by the instant specification. Thus, applicants assert that the claims are enabled and fully described and respectfully request the rejection be withdrawn.

Written Drescription

The Examiner also maintains the rejection of claims 1, 2 and 10-12 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Examiner also rejected claims 1, 2 and 10-12 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that

the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants respectfully traverse the rejection and maintain that the claims meet the written description requirements. Possession of a fusion protein comprising a first polypeptide comprising a sequence of amino acid residues that is at least 90% identical to residues 41 to 148 of SEQ ID NO:2 only requires the disclosure of SEQ ID NO:2 combined with the pre-existing knowledge in the art regarding the genetic code and its redundancies, as stated in the **Written Description Training Materials, Example 11: Percent Identity**, published March 25, 2008. The instant specification provides said zalpha11 Ligand sequences (i.e. SEQ ID NOS: 2 and 56), with a discussion of the state of the art referred to in the Written Description Training Materials, for one example, on pages 13-16.

When functional language is present in a claim, **Example 11** provides some guidance as well. The **Training Materials** set forth that in cases such as this where the claims recite "wherein the fusion protein binds a receptor as shown in SEQ ID NO:115", the specification should provide a correlation between the structure of genus of polypeptides to the function used to delineate the genus. The instant specification does that. It discloses both human and mouse zalpha11 Ligand sequences (SEQ ID NOS:1 and 2 for human and SEQ ID NOS: 55 and 56 for mouse), with guidance as to what structural elements are conserved; both within the family and between ligands that bind a common receptor subunit. The present application provided an analysis of zalpha11 Ligand teaching which amino acid residues would be essential for function. For example, on page 11, the specification states that amino acid residues 44, 47 and 135 (as shown in SEQ ID NO: 2) played an important role in zalpha11 Ligand binding to its cognate receptor. In fact, the disclosure provided the teaching for further identification of specific mutants that bound the receptor and did not signal or bound with a lower specificity (see, co-owned U.S. 6,929,932). Such teachings provide evidence that applicants were in possession and could recognize polypeptides that are within the genus of the claimed polypeptides. Moreover, the specification teaches structure and function correlations as described in detail above.

Applicants respectfully submit that the written description requirement for claims 1, 2 and 10-12 under under 35 U.S.C. § 112, 1st paragraph has been met. The level of skill and knowledge in the art would allow the skilled artisian to identify all claimed fusion proteins comprising a first polypeptide comprising a sequence of amino acid residues that is at least 90% identical to residues 41 to 148 of SEQ ID NO:2; when combined with the teachings of the specification. The specification discloses multiple sequences for family cytokines, two species of zalpha11 Ligand, regions of conservation, and critical binding residues. The specification correlates thse structural features to the function of the polypeptides. One skilled in the art would recognize that the applicants were in possession of the claimed invention as a whole at the time of filing, and therefore, applicants request the rejection be withdrawn and the claims allowed.

The Examiner maintains the rejection of claims 9-11 under 35 U.S.C. §112, first paragraph, alleging that the specification, while being enabling for composition of polypeptide of SEQ ID NO:2 or polypeptide comprising residues 32 to 162 of SEQ ID NO: 2 (zalpha11 ligand) does not reasonably provide enablement for a pharmaceutical composition comprising a polypeptide that is 90% or 95% identical to residues 32 to 162 of SEQ ID NO: 2 or residues 32 to 162 of SEQ ID NO: 2.

Applicants believe this rejection is an inadvertent error because claim 9 was withdrawn (now canceled) and there are no claims directed to pharmaceutical compositions, and respectfully request the rejection be withdrawn.

Double Patenting

The Examiner maintains the provisional rejection of claim 1 as claiming the same invention as that of claim 1 of copending Application No. 11/551,344.

Applicants are enclosing a copy of a letter for Express Abandonment under 37 CFR §1.138 in US Patent Application No. 11/551,344. Abandonment of said application obviates the need for a Terminal Disclaimer in the present case and places the case in condition for allowance. Applicants respectfully request that the Examiner send a Notice of Allowance.

The Examiner maintains the provisional rejection of claim 1 under 35 U.S.C. §101 as claiming the same invention as that of claim 1 of copending Application No. 11/551,368.

Applicants are amending claim 1 of Application No. 11/551,368 to cover a specific embodiment and thereby will eliminate the conflicting claim from this application. Applicants will provide the amended claims of Application No. 11/551,368 to the Examiner upon request.

The Examiner maintains the provisional rejection of claim 1 under 35 U.S.C. §101 as claiming the same invention as that of claim 1 of copending Application No. 11/551,362.

Applicants are amending claim 1 of Application No. 11/551,362 to cover a specific embodiment and thereby will eliminate the conflicting claim from this application. Applicants will provide the amended claims of Application No. 11/551,362 to the Examiner upon request.

The Examiner maintains the provisional rejection of claims 1, 10 and 12 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 of copending Application No. 11/551,820 in view of Beckman et al. (US Patent No. 5,573,924).

Applicants traverse this rejection. On September 29, 2006, the Examiner required the Applicants to a make an election under 35 U.S.C. §121 in the instant application. As a result of the Restriction Requirement, applicants elected Group I, ultimately resulting in the claims. Application No. 11/551,820, was filed as a divisional application under 35 U.S.C. §121, to encompass Group VI, fusion proteins comprising a polypeptide of SEQ ID NO:2 and immunoglobulin heavy chain constant regions. Thus, applicant should be afforded all the rights of 35 U.S.C. §121, and the application filed as a result of the requirement should not used as a reference against this application. Applicants respectfully request the rejection be withdrawn and the claims allowed.

Conclusion

In light of the above amendments and remarks, reconsideration and withdrawal of the rejections are respectfully requested. It is, thus, respectfully requested that claims 1, 2, and 10-12 are in condition for allowance and notification to that effect is respectfully requested. If for any reason the Examiner feels that a telephone conference would expedite prosecution of the application, the Examiner is invited to telephone the undersigned at (206) 442-6672.

Respectfully Submitted,

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